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Research Article

Catalytic Stereoselective 1,2-*cis*-Furanosylations Enabled by Enynal-Derived Copper Carbenes

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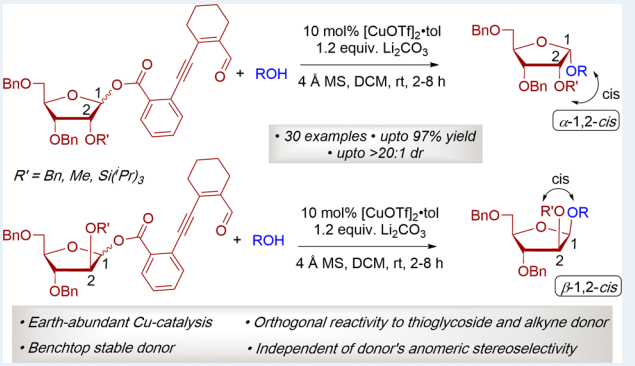
ABSTRACT: 1,2-*cis*-Furanosides are present in various biomedically relevant glycosides, and their stereoselective synthesis remains a significant challenge. In this vein, we have developed a stereoselective approach to 1,2-*cis*-furanosylations using earth-abundant copper catalysis. This protocol proceeds under mild conditions at room temperature and employs readily accessible benchtop stable enynal-derived furanose donors. This chemistry accommodates a variety of alcohols, including primary, secondary, and tertiary, as well as mannosyl alcohol acceptors, which have been incompatible with most known methods of furanosylation. The resulting 1,2-*cis*-furanoside products exhibit high yields and anomeric selectivity with both the ribose and arabinose series. Furthermore, the anomeric selectivity is independent of the C2 oxygen-protecting group and the anomeric configuration of the starting donor. Experimental evidence and computational studies support our hypothesis that copper chelation between the C2 oxygen of the furanose donor and an incoming alcohol nucleophile is responsible for the observed 1,2-*cis*-stereoselectivity.



KEYWORDS: *copper catalysis, 1,2-cis-furanosides, stereoselective glycosylation, enynal-derived metal carbenes, earth-abundant catalysis, carbohydrate chemistry*

INTRODUCTION

Carbenes are versatile synthetic intermediates capable of novel transformations, leading to the rapid generation of molecular complexity with high efficiency, selectivity, and atom economy.[1] Diazo compounds are commonly employed to generate these species by extruding elemental nitrogen. Other frequently used precursors include hydrazones, triazoles, sulfonium ylides, cyclopropenes, and alkynes (Figure 1a). These carbenes, or metal carbenoid species, readily partake in a range of synthetically appealing transformations, including cyclopropanations,[2] dipolar cycloadditions,[3] insertions into XH bonds (X = C, Si, O, S, N, etc.),[4] reactions with nucleophiles, as well as migratory insertions involving various metals.[5] Moreover, carbenes find applications in polymerization,[6] olefin metathesis,[7] and labeling biomolecules (including proteins, RNA, and DNA) for research and diagnostic purposes.[8] While carbenes have found diverse applications across multiple domains, their potential in carbohydrate chemistry has been largely untapped. Carbenes are, in fact, rarely utilized in glycoscience transformations.[9]

The first report on the utilization of carbenes in glycosylation goes back to 1989, when the Vasella group synthesized glycosylidene carbenes from the corresponding diazirines.[9a] Because of the instability of diazirines, they then employed the anomeric *N*-tosylhydrazone donors, which are benchtop stable carbene precursors. The sodium salts of these *N*-tosylhydrazones under photochemical conditions generate the corresponding anomeric carbenes, which undergo an O−H insertion reaction with alcohols to form *O*-glycosides (Figure 1b).[10] However, the glycosylidene carbenes generated from the sodium salts of *N*-tosylhydrazones require an excess of alcohol acceptors to synthesize *O*-glycosides. Additionally, product yields in these transformations were remarkably low, and the scope was found to be very limited. The same anomeric carbene has also been applied to protecting group-free phosphorylation.[11] The necessity for a substantial excess of nucleophiles restricted the use of these highly reactive anomeric carbenes in glycosylation; however, it paved the way for potential applications of carbenes to achieve stereoselective glycosylation. In 2019, the Wan group activated thioglycosides using rhodium carbenes (Figure 1c).[9m]

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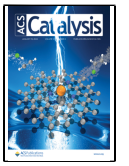

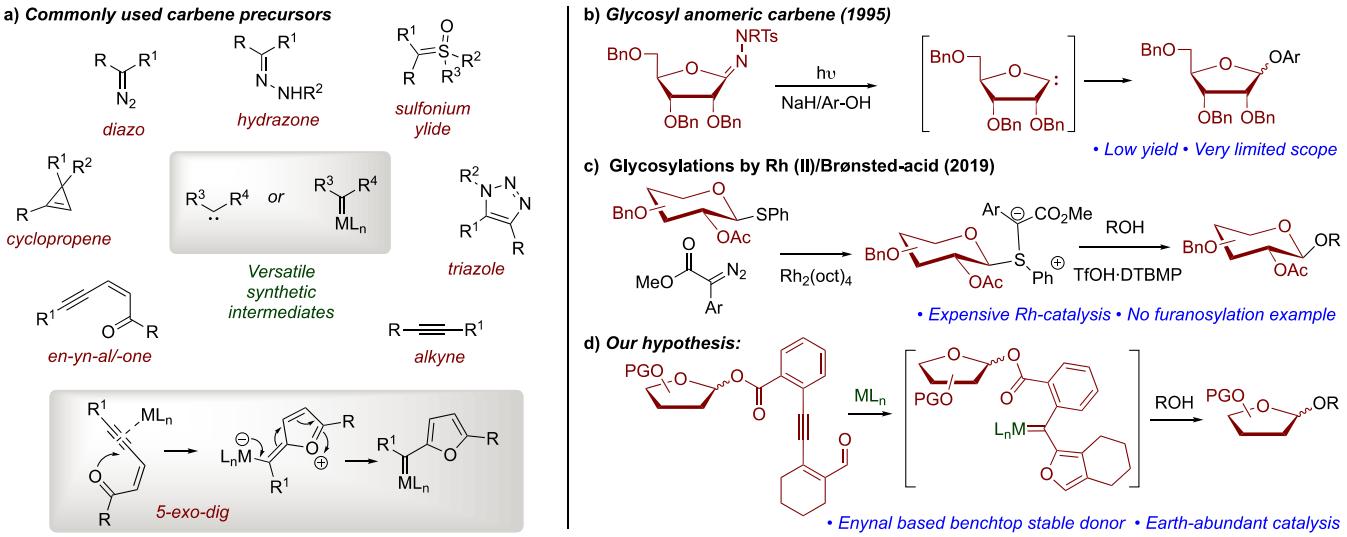

Figure 1. (a) Common carbene precursors. (b) Glycosyl anomeric carbene. (c) Catalytic glycosylation with Rh-carbene. (d) Our approach.

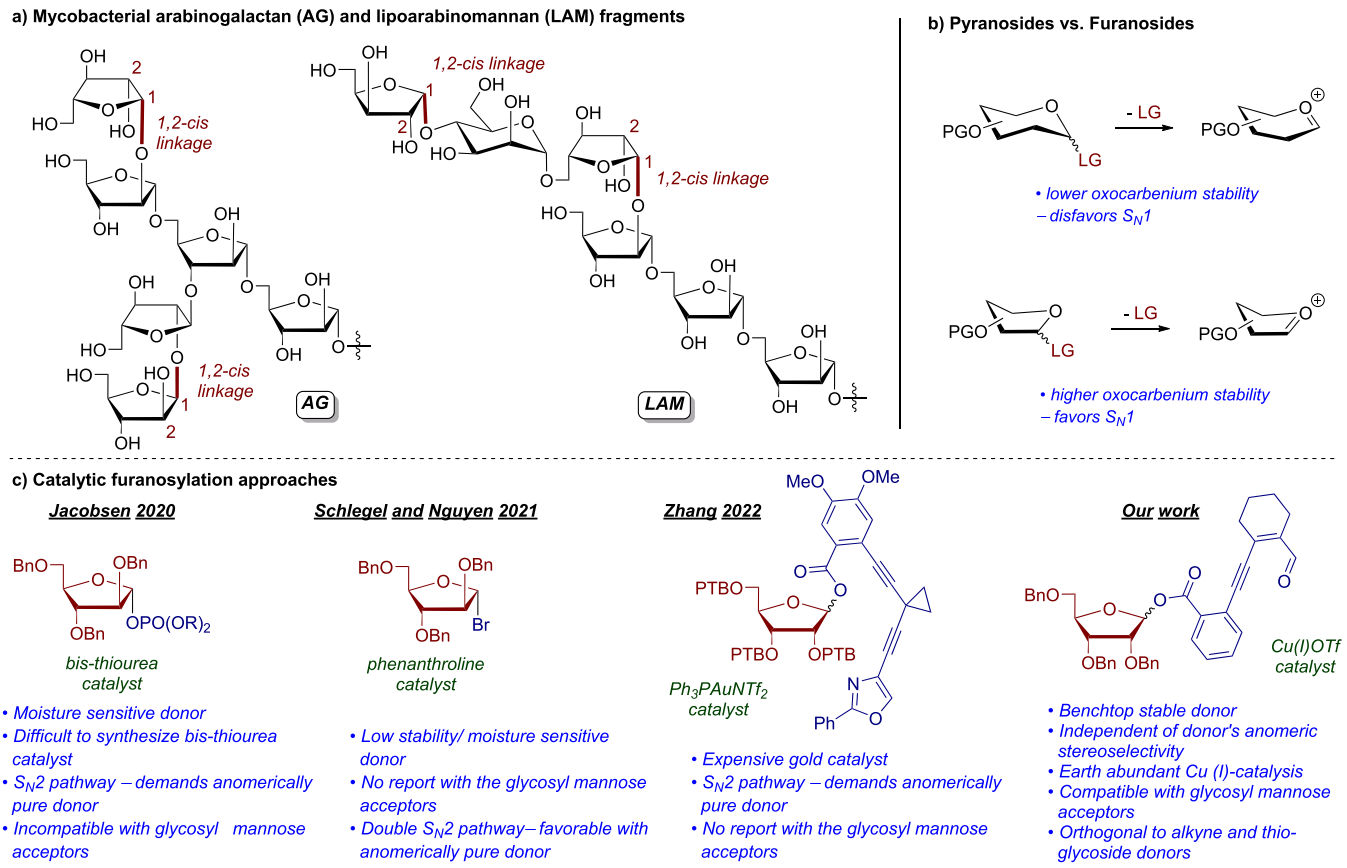

Figure 2. (a) Cell wall hexasaccharide motifs featuring 1,2-*cis*-furanosidic linkages. (b) Differences in reactivity between furanose and pyranose donors. (c) Catalytic furanosylation approaches.

This pyranosylation strategy lacks chemoselectivity and proceeds through two stages: initially, the generation of anomeric sulfonium ylides using a diazo-derived rhodium carbene, followed by protonation of the ylide to provide an oxocarbenium ion, which subsequently engages in glycosylation with alcohol acceptors.

Diazo compounds, however, are mainly activated by using precious rhodium catalysts and hold a reputation for their instability and the safety concerns associated with their regular use. Consequently, significant focus has been placed on identifying sustainable and safe alternatives for generating metal carbenes. Our search led us to the emerging field of enynal and enynone chemistry.[12] These carbene precursors comprise conjugated alkenes, alkynes, and aldehydes or ketones, thus en-yn-al/-one. These compounds maintain numerous benefits when compared to traditional carbene precursors like diazos. For example, these carbene precursors are easy to synthesize and far more stable due to the absence of

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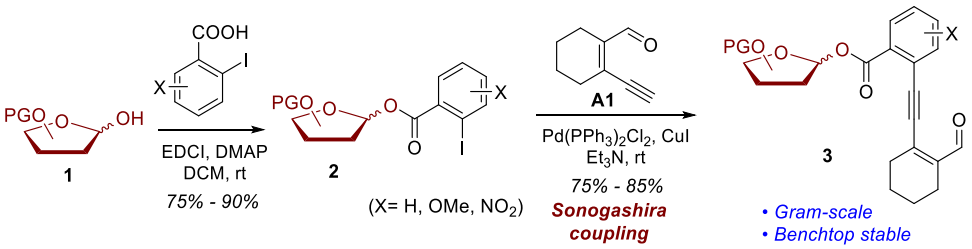
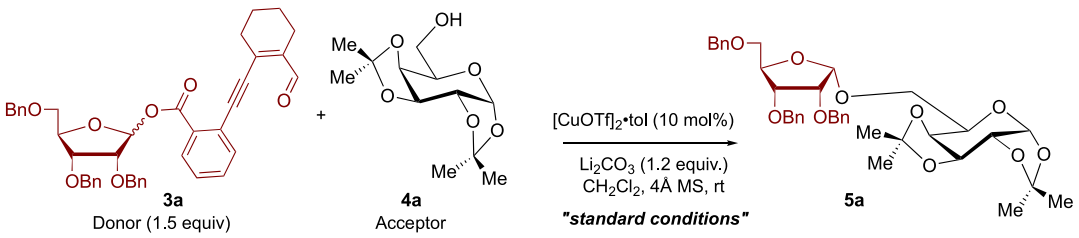


Figure 3. General synthesis of furanosyl enynal donors.

Table 1. Optimization of the Reaction Conditions[a]



entry	variation from the "standard conditions"	% yield[b]	time	α/β ratio[c]
1	none	78	4	7/1
2	$ZnCl_2$, no $[CuOTf]_2$·tol	20	36	1.5/1
3	$FeCl_3$, no $[CuOTf]_2$·tol	15	36	3/1
4	$ZnOTf_2$, no $[CuOTf]_2$·tol	n.r.	36	n.d.
5[d]	PPh_3AuOTf, no $[CuOTf]_2$·tol, no Li_2CO_3	56	3	7/1
6[e]	$Rh_2(esp)_2$, no$[CuOTf]_2$·tol, no Li_2CO_3	n.r.	36	n.d.
7	$Cu(MeCN)_4PF_6$, no $[CuOTf]_2$·tol	55	4	2/1
8	$Cu(MeCN)_4BF_4$, no $[CuOTf]_2$·tol	<10	24	n.d.
9	THF as solvent	n.r.	24	n.d.
10	ACN as solvent	n.r.	24	n.d.
11	toluene as solvent	<10	24	n.d.
12	TfOH, no Li_2CO_3, no $[CuOTf]_2$·tol	25	2	1/2.5
13	$[CuOTf]_2$·tol, no Li_2CO_3	50	4	5/1
14[f]	$[CuOTf]_2$·tol, DTBMP, no Li_2CO_3	46	10	5/1
15	no $[CuOTf]_2$·tol, Li_2CO_3 only	n.r.	36	n.d.

[a]All furanosylations were conducted with acceptor (0.05 mmol), donor (0.075 mmol), 10 mol % of catalyst, and 1.2 equiv of Li_2CO_3 with respect to the acceptor, CH_2Cl_2 (0.04 M). [b]Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]Diastereoselectivity was determined by ^1H NMR. [d]Catalyst was generated by premixing PPh_3AuCl and AgOTf, and the reaction was carried out at −15 °C. [e]Reaction was refluxed at 60 °C. [f]Reaction was heated at 40 °C. n.r. = no reaction; n.d. = not determined.

the high-energy dinitrogen (N_2) motif that causes diazo compounds to have a reputation for instability.[13] Additionally, enynals are recognized for their activation through transition metals via a 5-*exo*-dig cyclization process, leading to the formation of a furyl carbene. We hypothesize that the resulting furyl carbene, derived from enynals, would facilitate the activation of the furanose ester under mild conditions, enabling a stereoselective furanosylation process (Figure 1d).

Furanosides are key constituents of many biomedically relevant carbohydrates. Although less common than their pyranoside-based counterparts, oligo- and polyfuranosides are widely distributed in mammals, plants, bacteria, and parasites.[14] Because of their biological significance, there has been a growing interest in the stereoselective synthesis of furanose-containing glycans.[15] Furanosides are commonly identified as featuring 1,2-*trans* and 1,2-*cis* linkages in oligo-and polysaccharides, and the stereochemistry of these linkages is important for their biological function (Figure 2a). While assembling a 1,2-*trans* linkage through anchimeric assistance from a C2-*O*-acyl protecting group is relatively easy,[16] synthesizing the 1,2-*cis* linkage is much more challenging.[17] Furthermore, the higher stability of the oxocarbenium ion in furanosides when compared to their pyranoside counterparts favors the S_N1 end of the S_N1−S_N2 glycosylation boundary (Figure 2b),[18] making it more challenging to achieve 1,2-*cis*-selectivity in furanosides. Most glycosylation approaches developed for 1,2-*cis* linkages in the pyranoside system do not work well with the furanosides, and similar glycosyl donors in furanosylation reactions provide a mixture of stereoisomers. Several innovative approaches using stoichiometric reagents have been designed to overcome these inherent challenges, such as intramolecular aglycone transport,[19] donors with constrained conformations,[15c,20] and the use of functionalized *O*-protecting groups for hydrogen-bond-mediated aglycone transport.[21] Recently, a few elegant catalytic approaches to 1,2-*cis*-furanosylations have been introduced (Figure 2c). The Jacobsen group reported an elegant method for the activation of phosphorus-based furanoside donors using a bis-thiourea organocatalyst to access 1,2-*cis*-furanosides.[22] However, the bis-thiourea catalysts are difficult to synthesize and highly substrate-specific as they do not tolerate mannosyl alcohols as an acceptor. The group of Schlegel and Nguyen reported a

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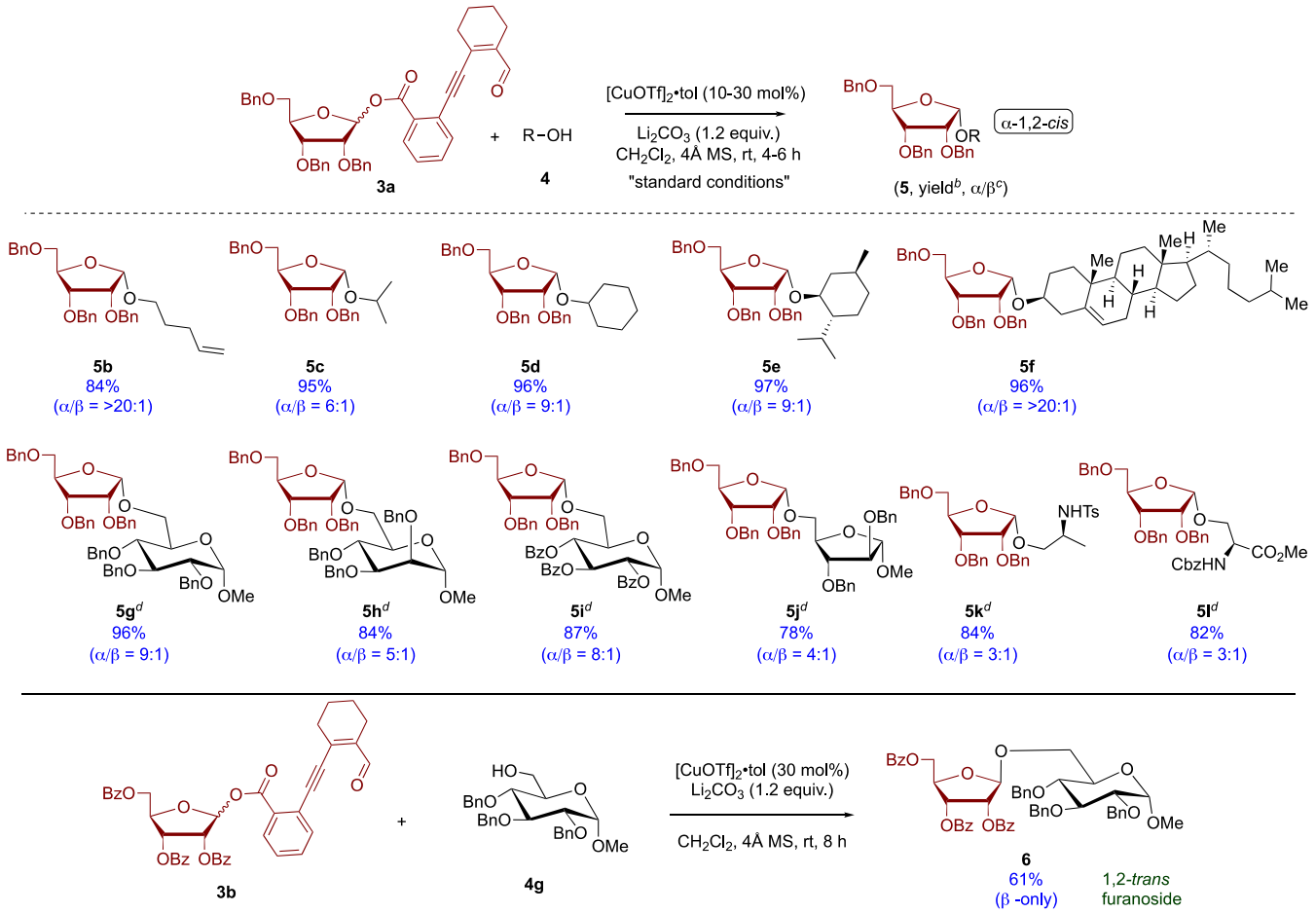
Table 2. Reaction of Alcohol Nucleophiles with D-Ribofuranosyl Donor[a]



[a]All furanosylations were conducted with donor (0.075 mmol), acceptor (0.05 mmol), 10 mol % of catalyst, and 1.2 equiv of Li_2CO_3 with respect to the acceptor, CH_2Cl_2 (0.04 M). [b]Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Diastereoselectivity was determined by ^1H NMR. [d]30 mol % of catalyst was used.

phenanthroline-supported 1,2-*cis*-furanosylation strategy in which a C1-bromo donor and a phenanthroline organocatalyst direct an acceptor to the *cis* face.[23] Likewise, halo donors are highly susceptible to hydrolysis and must be used immediately after their synthesis. Zhang and co-workers have recently developed an alkyne-based benchtop stable donor that is activated using precious gold-catalysis to undergo a stereoinvertive attack at C1 with an alcohol acceptor, resulting in the formation of 1,2-*cis*-furanosides.[24] Furthermore, these methods require an anomerically pure donor to achieve the desired 1,2-*cis*-selectivity.

To overcome these limitations, there is a need to design a donor where the 1,2-*cis*-selectivity is independent of the anomeric configuration of the donor. Additionally, the donor should have orthogonal reactivity to other donors and be activated using earth-abundant metals (iron, copper, and zinc) rather than precious rare-earth metals such as rhodium, gold, and palladium. Based on our group's experience in metal carbenes,[25] we endeavored to develop an earth-abundant metalcatalyzed carbene-based approach to 1,2-*cis*-furanosylation.

Our methodology commences by synthesizing simple and benchtop stable donors via straightforward EDCI-coupling of iodobenzoic acids with readily accessible anomeric alcohols **1**. The resulting esters **2** were coupled to the enynal moiety using a Sonogashira coupling to provide a variety of enynal donors **3** in high yields (Figure 3; see the Supporting Information for details).

We sought to optimize the reaction conditions by identifying the best component in the reaction in each of three categories: catalyst, acid scavenger, and solvent. We initiated our reaction optimization with the 2,3,5-tri-*O*-benzyl-*α*-D-ribofuranosyl donor **3a** and 1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranose acceptor **4a**. Through this study, we found that 10 mol % of copper(I) trifluoromethanesulfonate as the catalyst, lithium carbonate (1.2 equiv) as the acid scavenger, and CH_2Cl_2 as the solvent (0.04 M) at 25 °C with 4 Å molecular sieves led to the highest yield (78%) favoring the desired 1,2-*cis*-diastereoselectivity (7:1, Table 1, entry 1) in the shortest amount of time. Reactions were carried out using 1.5 equiv of the donor as the reaction conditions resulted in a small degree of unproductive decomposition of the donor. Initiating our optimization, we selected catalysts shown to activate enynal systems in the literature.[12f] The earth-abundant catalysts zinc(II) chloride and iron(III) chloride were found to decrease the yield and diastereoselectivity considerably and required more time to reach completion (entries 2 and 3). Other metal triflates, such as zinc(II) triflate and triphenylphosphine gold(I) triflate, did not appear to be effective. While zinc triflate yielded no reaction after 36 h (entry 4), gold triflate displayed a lower

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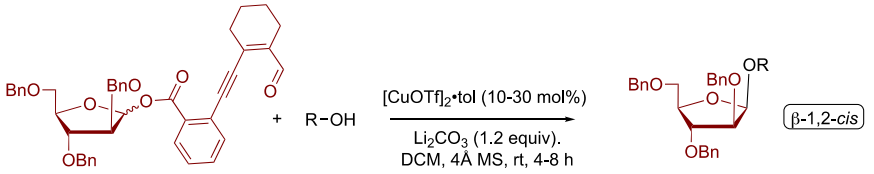
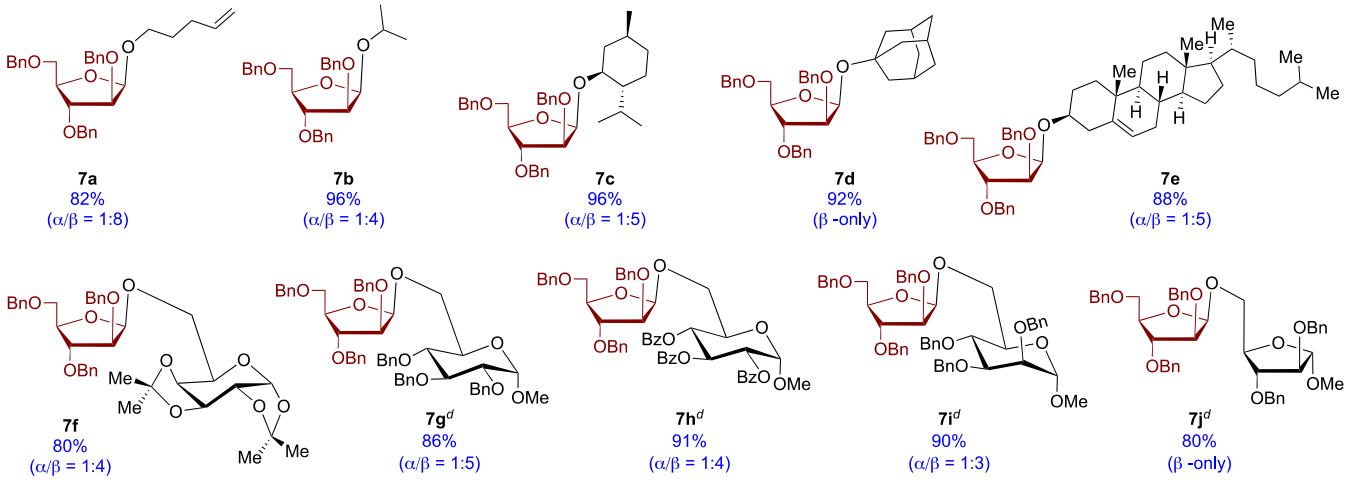
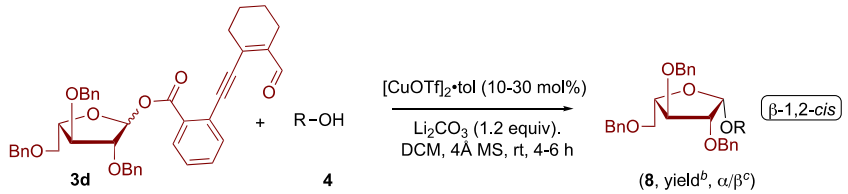
Table 3. Furanosyl Donor Scope[a]

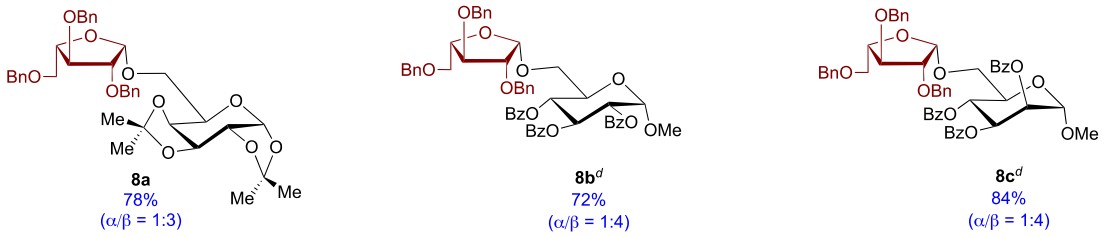
a) *Reaction of alcohol nucleophiles with D-arabinofuranosyl donor*





b) *Reaction of alcohol nucleophiles with L-arabinofuranosyl donor*





[a]All furanosylations were conducted with donor (0.075 mmol), acceptor (0.05 mmol), 10 mol % of catalyst, and 1.2 equiv of Li_2CO_3 with respect to the acceptor, CH_2Cl_2 (0.04 M). [b]Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Diastereoselectivity was determined by NMR. [d]30 mol % of catalyst was used.

yield but with comparable selectivity to the parent reaction (entry 5). $Rh_2(esp)_2$, which has also been documented to activate enynal compounds,[12f] was unable to initiate the furanosylation (entry 6). Next, we sought to investigate the effect of the counterion present on the copper(I) metal salt. When tetrakis(acetonitrile)copper(I) hexafluorophosphate was selected, the yield fell slightly; however, the selectivity dramatically decreased (entry 7). In the case of tetrakis-(acetonitrile)copper(I) tetrafluoroborate, the reaction proved to be sluggish and yielded nearly no product (entry 8). We then proceeded to optimize the solvent for this reaction. Lewis basic solvents such as THF and acetonitrile were found to produce no reaction, ostensibly due to the coordination of the solvent to the copper catalyst (entries 9 and 10). Toluene, however, did furnish the product, albeit in a significantly decreased yield (10%) and with no selectivity observed (entry 11). From here, we decided to perform control experiments to determine the necessity of each additive. As metal triflates are a mild source of triflic acid,[26] it cannot be discounted that triflic acid could catalyze this reaction. To evaluate this, we added triflic acid instead of lithium carbonate and Cu(I)OTf. In this case, we witnessed a significant decrease in the yield and a complete reversal of diastereoselectivity (entry 12). This result is in accordance with Sharma and Tan's work on $Sc(OTf)_3$-catalyzed spiroketalizations,[26d] where triflic acid can cause the partial decomposition or isomerization of the product from a kinetic product to a more stable thermodynamic product. To probe the impact of the acid scavenger, we executed the reaction without lithium carbonate, which decreased yield and selectivity, probably due to the generation of a small amount of

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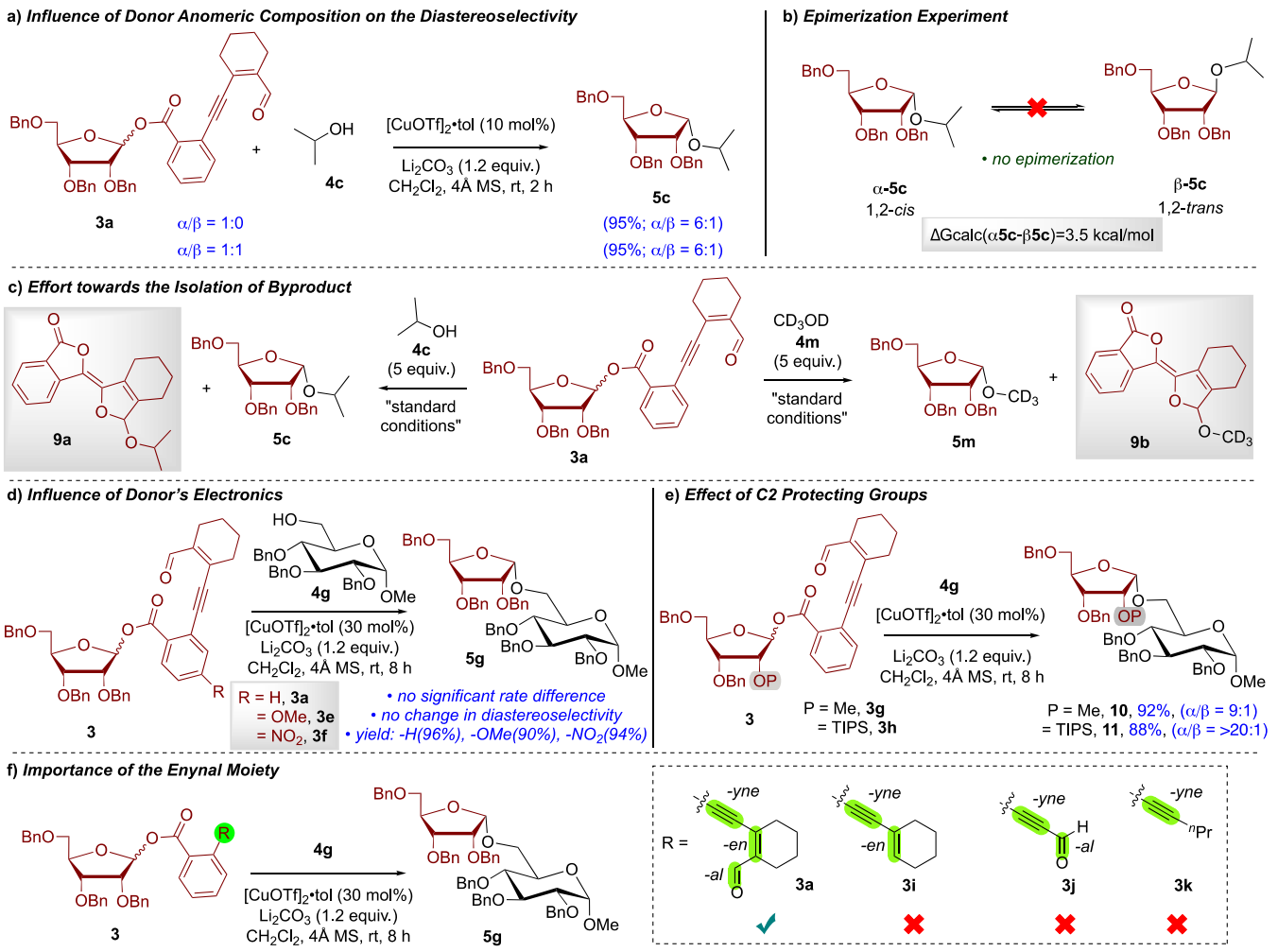

Figure 4. (a) Influence of the donor's anomeric composition. (b) Epimerization experiment. (c) Isolation of the byproduct. (d) Influence of donor electronics on stereoselectivity. (e) Effect of C2 protecting groups. (f) Significance of the donor's -en-yn-al functionality.

triflic acid in the system (entry 13). Selecting 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as an alternative acid scavenger led to further declines in output, presumably due to thermal decomposition induced by the higher reaction temperature (entry 14). Finally, we discovered that the presence of a copper catalyst is essential for the reaction to occur (entry 15).

With optimized conditions, a substrate scope consisting of arabinose and ribose donors was built out. A benzyl-protected D-ribofuranosyl donor was selected, and was reacted with various alcohol acceptors. A primary alcohol featuring a terminal olefin was examined. The reaction proceeded smoothly in a high yield with very high *α-cis*-selectivity (Table 2, **5b**). Secondary alcohols, such as isopropanol and cyclohexanol, proceeded rapidly to afford the corresponding products in a >95% yield with high *cis*-selectivity (**5c** and **5d**). Chiral secondary alcohols such as cholesterol and L-menthol were then subjected to the optimized conditions, yielding their respective products with excellent yield and *cis*-selectivity (**5e** and **5f**). It is worth noting that a nearly exclusive *α-cis*-product was observed in the case of cholesterol. Various carbohydrate alcohol acceptors bearing different protecting groups were also screened. Unlike previous acceptors, benzyl-/benzoyl-protected glucopyranosides, as well as benzyl-protected arabinofuranoside acceptors and protected amino acid alcohol acceptors, required higher catalyst loading to provide the intended products in sufficient yields. For example, 10 mol % of the copper catalyst with acceptor **4g** provides 64% yield of product **5g** with a significant amount of unreacted donor, while 20 mol % provides 82% and 30 mol % leads to almost quantitative conversion (96%). However, we did not observe any significant difference in 1,2-*cis*-selectivity. To our delight, reaction yields and selectivity were independent of protecting group influence for benzyl-/benzoyl-protected carbohydrate acceptors (**5g**−**5j**). Notably, the mannosyl acceptor, incompatible with the bis-thiourea catalyst,[22] worked equally well under our optimized conditions to provide the 1,2-*cis*-furanosylation product. Amino acid alcohol acceptors, including tosyl-protected alaninol and protected serine, were also examined, resulting in high yields and good *cis*-selectivity (**5k** and **5l**).

In addition, 1,2-*trans*-glycosidic linkages are also essential in carbohydrate chemistry as they are crucial in determining the biological activity and stability of various glycosides and polysaccharides.[27] Therefore, we decided to examine the compatibility of our optimized reaction conditions to access a 1,2-*trans*-furanosidic linkage via the assistance of neighboring-group participation. We were pleased to observe that benzoyl donor **3b** generated product 6 in a moderate yield (61%) with an exclusive *β-trans*-selectivity.

With the success of the ribose donor, we sought to investigate a substrate scope with an arabinose donor **3c**. 4-

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Penten-1-ol reacted effectively, yielding the desired arabinofuranoside **7a** with high yield and β-*cis*-selectivity (Table 3a, 82%, α/β = 1:8). Simple secondary alcohol isopropanol furnished product **7b** in a high yield with good stereoselectivity (96%, α/β = 1:4). Chiral secondary alcohol L-menthol as the acceptor led to a similarly high yield with even greater selectivity (**7c**, 96%, α/β = 1:5). Tertiary alcohol acceptor 1-adamantanol also resulted in an 88% yield, in line with those previously discussed and with exclusive β-*cis*-selectivity (**7d**, 92%). Similarly, cholesterol underwent a smooth reaction, yielding the corresponding product **7e** with a high yield and *cis*-selectivity. To our pleasure, acetonide, benzyl, and benzoyl-protected glucose acceptors proved facile and reactive in our system with high yields and β-*cis*-selectivity (**7f**–**7h**). As previously described, acceptors derived from mannose were unreactive with the Jacobsen bis-thiourea furanosylation protocol.[22]

To our delight, our method furnished the intended product with the arabinose donor in high yields and selectivity with the mannose acceptor (**7i**, 90%, α/β = 1:3). Finally, the benzyl-protected arabinofuranoside acceptor afforded the desired product **7j** in a respectable yield (80%) and with exclusive β-*cis*-selectivity. Furthermore, we noticed that the *cis*-selectivity of the newly formed furanosidic linkage was not affected by the reactivity of the nucleophilic acceptor. This was evidenced by electron-donating and electron-withdrawing acceptors affording their products with similar selectivity. To demonstrate the compatibility with an opposite enantiomer, L-arabinofuranoside was also examined as a donor with various alcohol acceptors. Reactions with donor **3d** displayed β-*cis*-selectivity, likewise, observed with D-arabinofuranoside. The acetonide and benzoyl-protected glucopyranoside acceptors supplied their intended products in good yield with modest selectivity (Table 3b, **8a** and **8b**). Similarly, the benzoyl-protected mannopyranoside acceptor provided the desired outcome with a good yield and selectivity (**8c**, 84%, α/β = 1:4).

Jacobsen and co-workers reported that the reaction outcome in their bis-thiourea-catalyzed furanosylation was significantly impacted by the anomeric composition of their furanose phosphate donors.[22] Recently, the Zhang group disclosed a gold-catalyzed alkyne donor for 1,2-*cis*-furanosylations,[24] wherein the stereoselectivity also depends on the anomeric purity of the initial donor. This is due to the underlying mechanism of S_N2-like displacement that requires an anomerically pure donor.

To determine the influence of the anomeric configuration of our donor on the stereochemical outcome of the developed protocol, a racemic mixture and an anomerically pure version of the D-ribofuranoside donor were synthesized and implemented in a head-to-head comparison (Figure 4a). Based on the observed results, it is apparent that 1,2-*cis*-diastereoselectivity is independent of the anomeric configuration of the donor, and the reaction proceeds through a common intermediate, ostensibly the oxocarbenium ion of the furanose donor, to produce the desired high 1,2-*cis*-selectivity. Additionally, we examined the epimerization of the α/β-furanoside products using the established reaction conditions (Figure 4b). The product exhibited no signs of epimerization, underscoring the stability and mildness of our developed protocol.

Through initial studies, we found the byproduct of this reaction to be unstable, and so we attempted to isolate an intermediate of the byproduct through a trapping experiment; the reaction was set up with ribose donor **3a** and an excess of alcohol acceptor isopropanol **4c** (5 equiv). We found that this resulted in the synthesis of the expected product **5c** and an isomerized isopropanol trapped byproduct **9a**. Additionally, we performed another reaction with deuterated methanol as the acceptor, and we were able to isolate similarly isomerized deuterated methanol incorporated byproduct **9b** along with product **5m** (Figure 4c) (see Supporting Information for more details).

To evaluate whether ester insertion into the carbene, which leads to the formation of the oxocarbenium ion, is the rate-determining step, we modified the electronic character of the aromatic ring on the donor. Subsequently, D-ribofuranosyl donors **3e** and **3f** were synthesized, featuring a methoxy and a nitro group para to the ester moiety in the aromatic ring. Our observations on the relatively similar rates of their reactions with acceptor **4g** (Figure 4d) led to the hypothesis that insertion of the ester into the generated carbene is not the rate-limiting step. Instead, we believe that the reaction rate depends primarily on the reactivity of the alcohol acceptor, which in turn depends on its steric and electronic properties. Thus, we can infer that the rate of formation of the oxocarbenium ion does not play a significant role in determining the rate of reaction. To investigate the effect of the C2 protecting group on the stereochemical outcome of this reaction, we synthesized ribosyl donors with modified C2 protecting groups (Figure 4e). As copper is known to coordinate with alkenes and alkynes, we replaced the C2 benzyl group with a non-π-aryl coordinating methoxy group (**3g**) to probe the role of the phenyl ring coordination in the benzyl protecting group. To our delight, there was no change in the stereochemical outcome of the product. Additionally, we employed a C2 silyloxy group (**3h**) to monitor coordination to the copper catalyst in ensuring *cis*-selectivity. When subjected to our parent conditions, we found that this silyloxy led to nearly exclusive *cis*-selectivity while maintaining high yields. This suggests that coordination of the copper catalyst to the C2 oxygen is necessary for the observed selectivity.

Subsequently, we explored the significance of the -en, -yn, and -al functionalities within our innovative furanosyl donor (Figure 4f). The absence of the aldehyde functionality in the synthesized en–yn ribosyl donor **3i** led to no reaction in the presence of the copper catalyst. Experimentation was also conducted with the ribosyl yn–al donor **3j**, which notably displayed a complete lack of reactivity in the desired furanosylation reaction. The well-established D-ribosyl -yn donor **3k** was unreactive under our standard reaction conditions. Nonetheless, the literature has shown that gold salts can activate these types of alkyne donors to initiate furanosylation.[28] This further highlights the importance of our copper carbene chemistry and the limitations of the known metal-catalyzed approaches, which require precious rare metals such as gold and rhodium. As described earlier, glycosylation catalyzed by earth-abundant metals has been notably missing from academic discourse, and many new donors are unreactive in the presence of such catalysts. These results also demonstrate the orthogonal reactivity of our donor to literature known alkyne donors, which could be harnessed for a one-pot iterative synthesis.

To further demonstrate the orthogonal reactivity of our donor, we attempted a reaction with propargyl alcohol as an acceptor to access propargyl donor **5n**, known to be reactive under gold(III) catalysis, as described by the Hotha group.[29] We were pleased to observe that the reaction exhibited full

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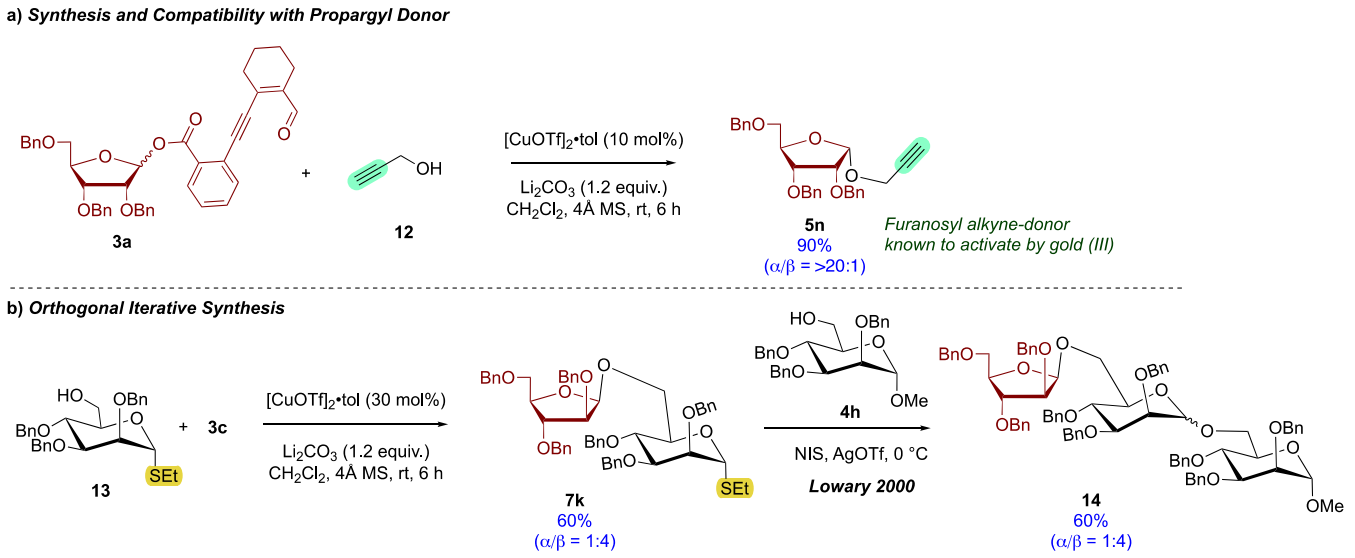

Figure 5. (a) Synthesis and compatibility with propargyl donor. (b) Orthogonal iterative synthesis with a thioglycoside acceptor.

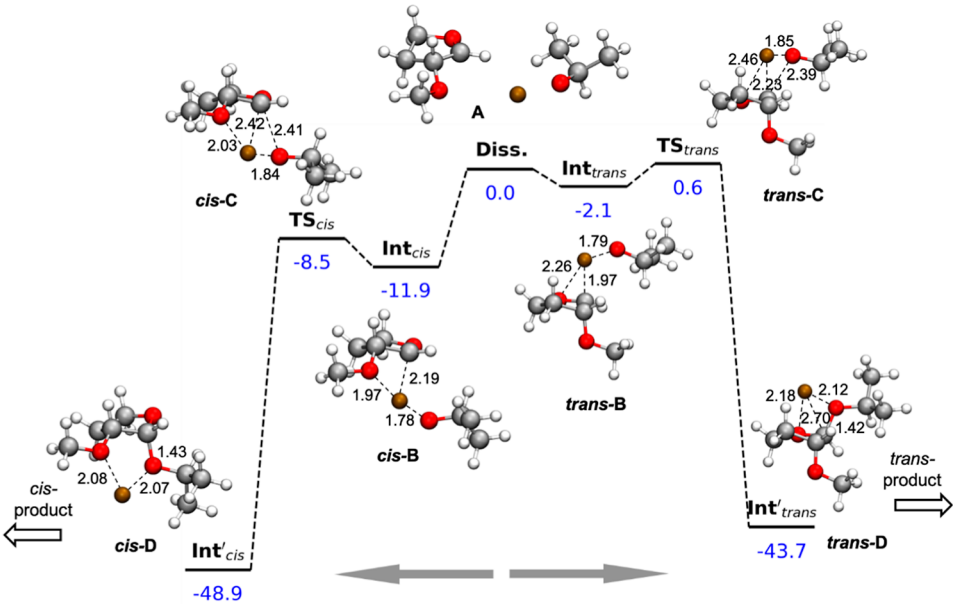

Figure 6. Free energy profile for the reaction of 2-OMe furan oxocarbenium ion with Cu(O^{i}Pr). Energies are given in kcal/mol; atomic distances are given in Å; and atomic colors: O = red, C = gray, H = white, and Cu = bronze.

compatibility with the alkyne group, furnishing a high product yield of 90% with near exclusive α-selectivity. This further highlights the selectivity of the copper catalyst for enynal donors over other alkyne donors known in the literature (Figure 5a).

We next demonstrated the orthogonal reactivity with well-established and widely utilized thioglycoside donors. As expected, acceptor **13**, bearing a thioglycoside moiety, reacted facilely under the optimized copper-catalyzed conditions, highlighting the orthogonal reactivity of these enynal donors. The newly formed thioglycoside product **7k** can be utilized in an established NIS/TfOH method to perform a one-pot iterative synthesis, as demonstrated by Lowary[30] (Figure 5b).

Results from the experimental study provided the following insights into the Cu-catalyzed reaction pathway: ionization of the ribose donor likely is not the rate-limiting step, and the *cis*-stereoselectivity is determined after this step. The latter point is supported by the noninterconvertibility of the isomeric products and the greater stability of the experimentally minor *trans*-isopropoxy product **5c** (ΔG_{calc} = 3.5 kcal/mol), as previously mentioned in Figure 4b. To computationally model the reaction pathway, we considered the likely copper-ligated species Cu(I)XY (X, Y = OR, OTf), which could attack the intermediate oxocarbenium ion. The reactant ratio for CuOTf/ROH/Li_2CO_3 of 0.1/1.0/1.0 and the Cu-anion binding affinities (see the Supporting Information for details) would favor the formation of species such as Cu(OR), Cu(OR)-$(OTf)^-$, and $Cu(OR)_2^-$.[31] Our DFT computational study[32] began by first considering the approaches of Cu-O^{i}Pr to either face of the model 2-methoxyfuran oxocarbenium ion A (Figure 6). Isomeric *cis*- and *trans*-C-bound Cu(III) alkoxide intermediates *cis*-B and *trans*-B, arising from oxidative addition, were found.[33] The *cis*-Cu(III)-C intermediate *cis*-B, which is stabilized by a bonding interaction with the adjacent -OMe

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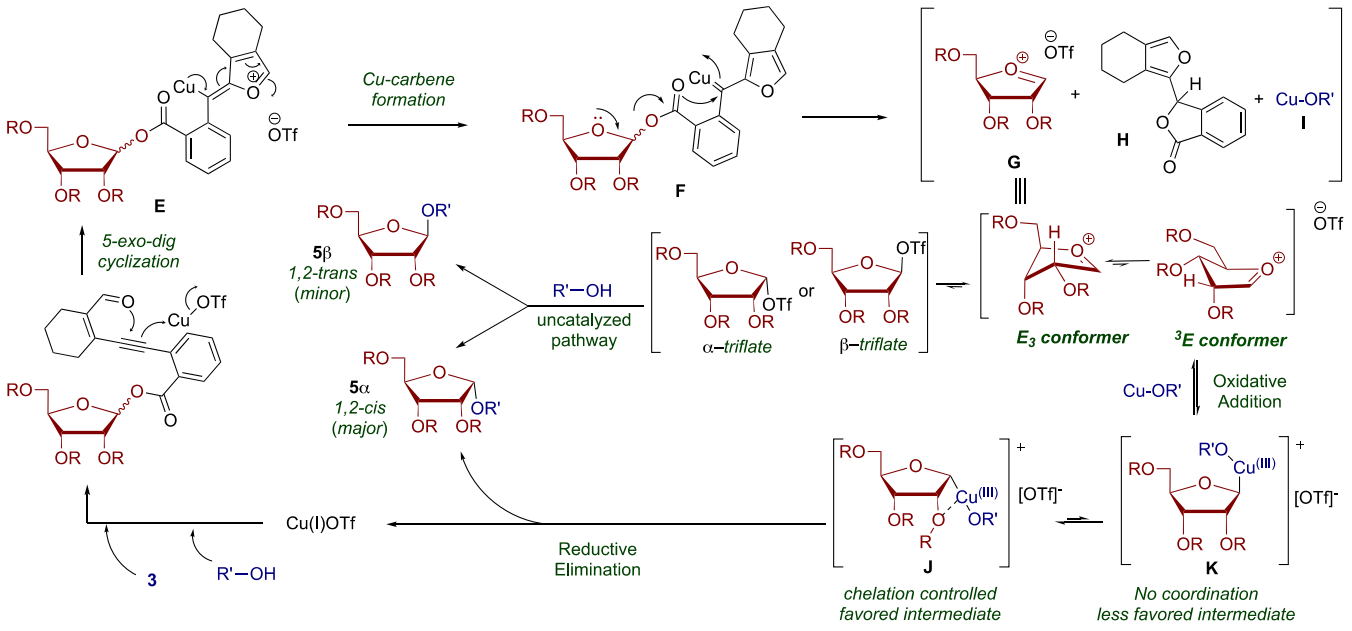

Figure 7. A plausible mechanism for copper-catalyzed ribofuranosylations.

group (Cu-OMe 1.97 Å, Cu-C 2.19 Å), is found to be 9.8 kcal/mol lower in energy (more stable) than the trans intermediate trans-B (Cu-O(furan) 2.26 Å, Cu-C 1.97 Å). Reductive elimination from the intermediates (*cis*-B, *trans*-B) leads to the respective cis- and trans-product complexes (*cis*-D, *trans*-D).[34] The transition states for this process (*cis*-C, *trans*-C) show the O−C bond-making and Cu-O-^{i}Pr bond-breaking: *cis*-TS: Cu-OMe 2.09 Å, Cu-C 2.42 Å, and C-O(^{i}Pr) 1.84 Å; trans-TS: Cu-O (furan) 2.46 Å, Cu-C 2.26 Å, and C-O(^{i}Pr) 1.85 Å. The activation energies for these isomeric transition states are small and quite similar, 3.4 vs 2.8 kcal/mol. According to the energetic profile of Figure 6, the *cis* product complex *cis*-D (and its Cu-free product **5c**) should be the exclusive product. This is qualitatively, but not quantitatively, in agreement with the experimental results. To reconcile the computational and experimental results, we also considered the stereoselectivity of the model carbocation reacting with $Cu(O^{i}Pr)(OTf)^{-}$ and $Cu(O^{i}Pr)_2^{-}$. With these $CuXY^{-}$ species, the *cis*-oxidative addition intermediate *cis*-B′ (Supporting Information) was only slightly favored or equal energetically to the *trans*-B′ by 0.3 kcal/mol for $-Cu(O^{i}Pr)(OTf)^{-}$ and −0.0 kcal/mol for $-Cu(O^{i}Pr)_2^{-}$. The longer *cis*-Cu-OMe and *trans*-Cu-O(furan) interactions in these cases (see Supporting Information for details) apparently are weaker, probably accounting for their similar stabilities. With both of these $CuXY^{-}$ species, the trans activation energy is comparable to, or lower (0.5−2.0 kcal/mol) than, the *cis* pathway, predicting a slight preference for the *trans* product. The involvement of these additional pathways would lower the observed cis-selectivity, as would competition with off-the-metal-alcohol attack directly on the oxocarbenium ion.

Based on the above-described results, control experiments, and computational calculations, we hypothesized a plausible mechanism for this copper-catalyzed 1,2-*cis*-furanosylation, as depicted in Figure 7. First, the enynal moiety in the presence of the copper(I)-catalyst forms intermediate E via a 5-*exo*-dig-cyclization. This process is followed by the back-donation from copper, leading to the aromatization of the furan moiety, thereby generating the copper-carbene, intermediate F. The resulting copper carbene activates the anomeric ester to form an oxocarbenium ion G, which is the common intermediate regardless of the anomeric configuration of the starting donor. The resulting oxocarbenium ion G can adopt both E_3 and ^{3}E conformations. Based on the literature, E_3 is identified as the more stable conformation, and an inside attack from the nucleophile to E_3 produces the *cis*-isomer.[35] The furan byproduct H, containing copper, undergoes protodemetalation with the acceptor alcohol, resulting in the formation of copper alkoxide I. This copper alkoxide then undergoes oxidative addition, leading to the formation of intermediates J and K. In the case of intermediate J, stabilization occurs through chelation between the C2 oxygen and copper. In contrast, no such stabilization is observed in intermediate K. Consequently, intermediate J is determined to be more stable than intermediate K. Ultimately, reductive elimination from intermediate J gives rise to the corresponding contra-thermodynamic 1,2-*cis*-furanosylation product (5α). On the other hand, the noncoordinated intermediate K can lead to the corresponding β-1,2-*trans*-product (5β). This proposed mechanism is further supported by the optimization results outlined in Table 1, where the use of the Cu(I)OTf catalyst resulted in a high degree of *cis*-stereoselectivity compared to triflic acid, suggesting the involvement of copper in providing the high anomeric 1,2-*cis*-stereoselectivity. Notably, oxocarbenium intermediate G can also exist in equilibrium as a contact-ion pair. The proximal triflate anion shields the α-face (α-triflate) or β-face (β-triflate) of the furanosyl oxocarbenium ion. A subsequent S_N2 attack on the α-triflate or the β-triflate species would furnish the β- or the α-furanosyl product (5), respectively, without the involvement of the copper catalyst.

CONCLUSIONS

In conclusion, an earth-abundant copper-catalyzed stereoselective furanosylation strategy is developed to access the challenging 1,2-*cis* furanosidic linkages.

This transformation proceeds at room temperature and provides high yields and excellent *cis*-stereoselectivity by utilizing novel benchtop stable enynal-derived furanosyl

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donors. This chemistry accommodates primary, secondary, and tertiary alcohol acceptors, as well as other furanose donors with different substitution and stereochemical patterns. Our control experiments indicate that the observed 1,2-*cis*-stereoselectivity is independent of the anomeric configuration of the starting furanose donors. This method also exhibits orthogonal selectivity with well-established alkyne and thioglycoside donors, enabling a one-pot iterative synthesis. Through experimental and computational studies, we have established that the desired *cis*-stereoselectivity arises from chelation between the C2-oxygen of the furanose donor and the incoming copper alkoxide nucleophile. These findings emphasize the unique capabilities of earth-abundant copper as a catalyst for highly stereoselective furanosylation reactions. Furthermore, applications of this method to other glycosylation reactions are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c05237.

Experimental procedures, NMR spectroscopic, and analytical data for all compounds (PDF)

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have given their approval to the final version of the manuscript.

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Notes

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